Rate of Hypokalemia and Risk Factors in Patients on Peritoneal Dialysis Under PD First Policy

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Abstract

Background: Hypokalemia is common among peritoneal dialysis (PD) patients. The incidence rate of hypokalemia and risk factors were investigated.

Material and Method: A retrospective cohort, enrolled 1,044 incident PD patients under the Universal Health Coverage(UHC) Scheme of a regional hospital between January 2012 and December 2018. Hypokalemia was defined as having serum potassium less than 3.5mEq/L. The rate of hypokalemia in episodes per one year at risk was determined. Risk factors of hypokalemia were reported as an incidence rate ratio using Poisson regression.

Results: The incidence rate of hypokalemia was 2.21(95% confidence interval, 2.14-2.27)episodes per one year at risk. Risk factors of hypokalemia were ; older than 60 years, female, diabetes, bodyweight less than 45 kg, serum albumin less than 3.5 g/dL, serum phosphate less than 2.5 mg/dL, and total lymphocyte count less than 1,500 cells/mm^3.

Conclusions: Hypokalemia was frequently occurred in PD patients. Elderly PD patients, female, diabetes, malnutrition, low serum albumin, and lowserum phosphate had higher risks to develop hypokalemia.

Keywords: *Electrolyte, potassium, hypokalemia, dialysis, peritoneal dialysis, CAPD PD First, Thailand.*

Introduction

The prevalence of hypokalemia in peritoneal dialysis (PD) patientsare previously reported between 10 to 36%[(1-6)]. Hypokalemia at baseline and time-average of serum potassium less than 3.5 mEq/L demonstrated its association with an elevated risk of mortality, particularly from cardiovascular and infectious-related causes[(5-9)]. Previous studies showed that malnutrition is an important factor correlated with low serum potassium levels in PD[(5,10,11)]. Daily potassium loss in dialysate, potassium loss from diarrhea, intracellular potassium shift stimulated by increases in blood levels of insulin release due to continuous glucose absorption from peritoneum infused with glucose-based peritoneal fluid, and usage of furosemide diuretic especially in patients with high residual renal function may additionally contribute to the development of hypokalemia in patients on PD[(6, 12-15)].

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There is a wide range in the prevalence of hypokalemia from previous studies. It may depend on the different populations studied, time of serum potassium measurement, and management of hypokalemia. PD First policy in Thailand was implemented in 2008 to provide dialysis for Thai patients with end-stage renal disease (ESRD) under the universal health coverage (UHC) scheme. According to this policy, there is a dramatic increase in the number of patients on PD. Our previous study showed that most of these patients had low educational levels and low socioeconomic status. The rate of PD patients with preexisting diabetes was higher than those in other Asia-Pacific countries [16]. The occurrence of hypokalemia in these patients may differ from others as they may have preexisting malnutrition, comorbid conditions, and inability to intake enough dietary potassium which, in consequence, may lead to a high chance for hypokalemia. To our knowledge, the magnitude of the incidence of hypokalemia in the PD cohort has not been investigated. The objectives of this study were to analyze the incidence rates of hyperkalemia and to identify risk factors associated with hypokalemia in PD patients under the UHC Thai PD First policy.

Materials and Method

Study population: PD patients, older than 15 years of age, under UHC schemein Chaiyaphum Hospital between January 2012 and December 2018 were recruited into the cohort. There were initially 1,215PD patients, 171 cases were excluded from being younger 15 years of age and incomplete electrolyte results. The final number of patients enrolled in the study was 1,044 cases.

Data collection and variables: The clinical and laboratory variables for analysis were gender, age at starting PD, diabetic status before initiating dialysis, date at start PD, date at the drop out from PD, bodyweight at the start of PD (BW), blood urea nitrogen (BUN), serum creatinine (SCr), serum albumin, serum phosphate, serum potassium and total lymphocyte count (TLC). Interested factors were gender, age at start PD, and diabetic status before initiating PD for investigating their association with serum potassium since they were factors related with patient survival in our previous study[16].

Definition and timing of hypokalemia, rates of hypokalemia per one year at risk, and defined risk factors from variables: Serum potassium level less than 3.5 mEq/L (<3.5 mEq/L)was defined as hypokalemia[1, 5]. It was measured at every two-month visit. Patients who had serum potassium measured and the level was <3.5 mEq/L more than one time in 2 months, they were counted as having one hypokalemia episode to avoid the high occurrence of hypokalemia from too often potassium measured. We did not use the time-averaged serum potassium in the entire cohort because it might be higher than 3.5 mEq/L from the calculation. For example, the time-averaged serum potassium was 3.8 mEq/L ina patient who had six values of serum potassium levels as 4, 3, 4, 3.6, 5, and 3 mEq/L. However, this patient had 2 episodes of hypokalemia based on the number of events that occurred. The rate of hypokalemia that occurred in episodes per one year at risk was determined by dividing the number of episodes of developing hypokalemia with the cumulative time on the treatment of PD patients. The time on therapy for each patient was calculated from the first date of continuously starting PD to the date of drop out or the last day of December 2018.

Gender, age at start PD, body weight, diabetic status, serum albumin, serum phosphate, and TLC were categorized into groups to identify the risk of developing hypokalemia. They were classified as the followings; male vs female, age younger and equal to 60 years vs older than 60 years, BW less than 45 kilograms (kg) vs equal to or higher than 45 kg, yes vs no diabetic status, serum albumin less than 3.5 g/day vs equal to or higher than 3.5 g/dL, serum phosphate less than 2.5 mg/day vs equal to or higher than 2.5 mg/dL and TLC less than 1,500 cells/mm3 vs equal to or higher than 1,500 cells/mm3. BUN, SCr, serum albumin, serum phosphate, and TLC were calculated at baseline which were the results recorded in the first three months of initiating PD and the averaged levels of those variables at the entire cohort to compare the results with each categorical risk factors.

Statistical analyses: The data were analyzed using the Stata software version 14.2 (serial number 501406216647, StataCorp, College Station, TX, USA. Categorical variables were demonstrated as frequency and percentage. Continuous variables were presented as mean and standard deviation. The rates of hypokalemia episodes per one year at risk were calculated for the median with 95% confidence interval (CI) which were analyzed based on the normal approximation to the binomial distribution. Risk factors of the rate of hypokalemia were shown as an incidence rate ratio (IRR) using Poisson regression analysis. A p-value of less than 0.05 was defined as statistical significance.

Results

Demographic and baseline clinical parameter of patients of 1,044 PD patients, proportion of male to female gender were 486 (46.74%)to 556 (53.26%) respectively. The proportion of diabetes before starting PD was 51.95%.

The mean (SD) of BW, BUN, SCr, serum albumin, serum phosphate and TLC in cells/mm^3 at baseline were 58.04 (10.31) kg, 58.10 (17.69) mg/dL, 14.23 (6.70) mg/dL, 3.31 (0.63) g/dL, 4.96 (2.07) mg/dL and 1,606.52 (719) cells/mm^3 respectively. The mean (SD) time of the treatment was 21.59 (18.49) months. The demographic and baseline of clinical parameters of patients were presented in Table 1.

Table 1 Demographic and baseline clinical characteristics of patient population

Characteristic	Value
Gender	
Number of male (%)	488 (46.74)
Number of female (%)	556 (53.26)
Age at start PD (years)	
Mean (SD)	56.18 (12.87)
Body weight (kilogram)	
Mean (SD)	58.04 (10.31)
Diabetic status before initiate dialysis	
Number (%)	542 (51.92)
Blood urea nitrogen (mg/dL)	
Mean (SD)	58.10 (17.69)
Serum creatinine (mg/dL)	
Mean (SD)	14.23 (6.70)
Serum albumin (g/dL)	
Mean (SD)	3.31 (0.63)
Serum phosphate (mg/dL)	
Mean (SD)	4.96 (2.07)
Total lymphocyte count (cells/mm3)	
Mean (SD)	1,606.52 (719.00)
Time on therapy (months)	
Mean (SD)	21.59 (18.49)

Rate of hypokalemia per one year at risk and risk factors: Table 2 shows the rates of hypokalemia episodes per one year at risk. There were 4,143 (36.7%) episodes of hypokalemia occurred in 11,291 events of follow up time every two months during 1,881.77 years of cumulative time on therapy. The incidence rate of hypokalemia was 2.21 (95% CI, 2.14-2.27) episodes per one year at risk. Patients who were older than 60 years of aged at the start of PD, female gender, BW less than 45 kg, having diabetes before PD, serum albumin less than 3.5 g/dL, and serum phosphate less than 2.5 mg/dL had significantly higher rates of hypokalemia per one year at risk than the other groups.

Risk factors of hypokalemia among PD patients were ; older than 60 years of aged at starting the start of PD, female gender, BW less than 45 kg, having diabetes before PD, serum albumin less than 3.5 g/dL, serum phosphate less than 2.5 mg/dL, and TLC less than 1,500 cells/mm^3 (Figure 1).

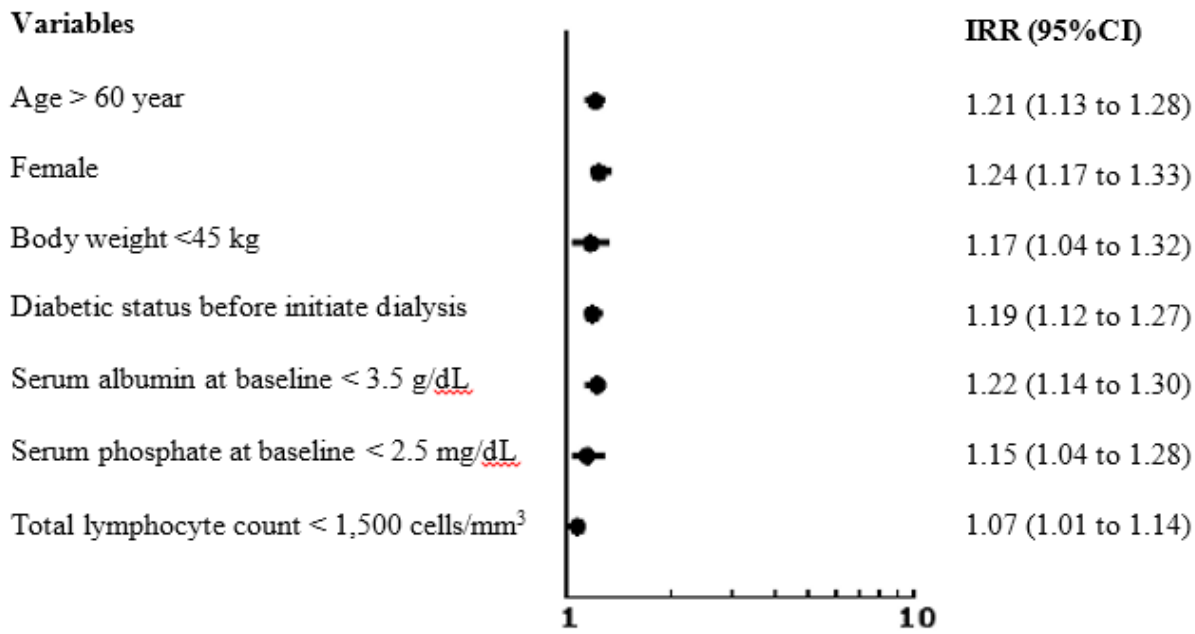
Levels of nutritional parameters and risk factors: The averaged levels of BUN, SCr, serum albumin, serum phosphate, and TLC of the entire cohort were shown in Table 3. Patients who were older than 60 years old, female gender, BW less than 45 kg, and having diabetes before PD,had lower levels of BUN, SCr, and serum phosphate than the other group. In addition, these patients except those with had BW less than 45 kg had lower levels of serum albumin than the others.

Table 2: Rate per year at risk for developing hypokalemia in each factors

Factor	Number of patients	Number of events	Person-time (year)	Rate per 1-year at risk	95%CI	P-Value
Overall	1,044	4,143	1881.81	2.21	2.14 to 2.27	
Age (years)						
Age >60	421	1,709	676.83	2.52	2.41 to 2.65	<0.001
Age ≤60	623	2,434	1,204.99	2.02	1.94 to 2.10	

Factor	Number of patients	Number of events	Person-time (year)	Rate per 1-year at risk	95%CI	P-Value
Gender						
Female	556	2,551	1,035.62	2.46	2.37 to 2.56	<0.001
Male	488	1,592	846.20	1.88	1.79 to 1.98	
Body weight (kg)						
<45	68	314	114.99	2.73	2.44 to 3.05	<0.001
≥45	976	3829	1,766.83	2.17	2.10 to 2.24	
Diabetic status						
Yes	542	2,238	896.33	2.50	2.39 to 2.60	<0.001
No	502	1,905	985.49	1.93	1.85 to 2.02	
Serum albumin (g/dL)						
<3.5	594	2,427	984.59	2.46	2.37 to 2.57	<0.001
≥3.5	450	1,716	897.22	1.91	1.82 to 2.01	
Serum phosphate (mg/dL)						
<2.5	82	437	156.59	2.79	2.54 to 3.07	<0.001
≥2.5	962	3,706	1,725.23	2.15	2.08 to 2.22	
TLC						
<1,500	518	2,115	978.74	2.16	2.07 to 2.26	0.216
≥1,500	526	2,028	903.08	2.25	2.15 to 2.35	

Abbreviation: TLC; total lymphocyte count (cells/mm^3)



Abbreviations: IRR, Incidence rate ratio; CI, Confidence interval

Figure 1: Incidence rate ratio of risk factors for developing hypokalemiain multivariate analysis

Table 3: Blood urea nitrogen, creatinine, albumin, phosphate and total lymphocyte count levels classified in age at start PD, gender, body weight and diabetic status

Factor	BUN (mg/dL) Mean (SD)	Creatinine (mg/dL) Mean (SD)	Albumin (g/dL) Mean (SD)	Phosphate (mg/dL) Mean (SD)	TLC* Mean (SD)
Age at start PD					
Age > 60 years	68.48 (43.37)	9.00 (2.91)	3.22(0.66)	4.53(1.85)	1,576.69 (711.87)
Age ≤ 60 years	73.80 (50.82)	11.26 (3.66)	3.37 (0.61)	5.26 (2.16)	1,626.68 (723.65)
Gender					
Female	64.77 (40.70)	9.28 (2.85)	3.29 (0.62)	4.61 (1.86)	1,681.81 (768.93)
Male	79.50 (54.15)	11.57 (3.88)	3.33 (0.65)	5.37 (2.22)	1,520.75 (647.71)
Body weight (kg)					
< 45 kg	71.25 (45.64)	9.12 (3.14)	3.38 (0.70)	4.59 (2.09)	1,668.23 (1,132.70)
≥ 45 kg	71.68 (48.19)	10.44 (3.57)	3.31 (0.63)	4.99 (2.07)	1,602.22 (681.59)
Diabetic status					
Yes	61.08 (41.65)	9.08 (2.81)	3.22 (0.59)	4.73 (1.96)	1,670.04 (725.84)
No	83.07 (51.70)	11.72 (3.76)	3.41 (0.67)	5.22 (2.15)	1,537.95 (705.86)

*Cells/mm^3

Discussion

This is the first study that demonstrated the incidence rates of hypokalemia occurred per one year at risk of PC patients under the UHC First PD policy in PD patient cohort. In previous studies, the time-averaged serum potassium, instead of the average potassium, was used to calculate for hypokalemia due to serum potassium changes followed the time on PD[9, 17]**.**Using the time-averaged serum potassium might observed fewer occurrence of hypokalemia than the actual events. In clinical practice, potassium supplement is prescribed to correct hypokalemia and serum potassium may turn to normal or higher in the next measurement**.** Using the time-averaged serum potassium levels may not reveal hypokalemia in this situation. This is the reason why we reported the incidence of hypokalemia by calculating the rate of events occurred per one year at risk, not using the time-averaged serum potassium, in this PD cohort**.** We counted the episode of hypokalemia occurred at every two months visit according to the process of follow up time in our PD clinic**.** We found that nearly 90% of PD patients had at least one episode of hypokalemia during their PD treatment courses. The incidence rate of hypokalemia (<3.5 mEq/L) was 2.21 episodes per one year at risk.

The results in our study demonstrated 88.7% of the patientshad at least one episode of hypokalemia. It confirmed previous studies that hypokalemia is common in PD patients[1,5,10]**.** The rate of hypokalemia at 2.21 episodes per one year at risk meant one patient could have hypokalemia nearly every six months of the follow-up visits. There are reasons to explain the development of hypokalemia in our study. First, our patients had averaged serum albumin levels less than 3.5 g/dL in the entire cohort. It indicated that our patients would have similarrisk of developing hypokalemia with previous studies, observing the association between serum potassium and poor nutritional status[11,18]. Second,there was a high proportion of patients with preexisting diabetes (51.9%) when compared with those in others (less than 50%)[1, 7-10,17]. It demonstrated that patients with preexisting diabetes had significant higher rate of hypokalemia per one year at risk than those without (2.50 vs 1.93 episodes per one year at risk, respectively). Hypokalemia was more likely to occurred in patients with preexisting diabetes-related, who were not only had poor nutritional status but also had chronic inflammation from coexisting comorbidities [5]. The levels of BUN, SCr, serum albumin, and serum phosphate were lower preexisting diabetes patients when compared with those without diabetes. Furthermore, the number of TLC which represented the immunological process, was higher among patients with preexisting diabetes. These results are supported by our observations. Third, our patients had the lower baseline serum albumin and serum phosphate levels than those in previous studies[7, 9, 10]. It meant most of our patients had poor nutritional status before starting dialysis. This might be related to late start of PD since our patients had higher levels of baseline SCr when compared with previous studies[1, 9, 10].

The risk factors of a high incidence of hypokalemia in our study were elderly at the start, female gender, underweight, had preexisting diabetes, low serum albumin at baseline, low serum phosphate at baseline, as well as low TLC. The rates of hypokalemia occurred in patients with these risk factors except for TLC. TLC less than 1,500 cells/mm^3 were significantly higher than those patients without these risk factors. Patients with these risk factors might have preexisting malnutrition before initiation of PD which persisted and increased severity after performing PD. The evidence showed the persistence and increased severity of poor nutritional status was the lower levels of BUN, SCr, serum albumin, and serum phosphate during the entire cohort among elderly, female gender or underweight. The presence of persisted and increased severity of malnutrition could be the reasons to explain the high incidence of hypokalemia in these patients**.**

Hypokalemia is related to poor nutritional status, of which our study was indirectly implied that malnutrition was a major problem among UHC-PD patients. It may be related to poverty, low education level, and low socioeconomic status[19]. Other possible causes of malnutrition among PD patients were related to the dialysis process such as protein loss in PD solution, abdominal fullness from PD fluid infused in the abdominal cavity, peritonitis, or volume overload [20-23]. Hypokalemia per se may be one factor that aggravates the persistence of poor nutritional status after PD from bowel ileus. Besides, hypokalemia was shown as being an independent risk factor of peritonitis in patients on PD[1]. Therefore, we propose the potassium supplementation should be prescribed for a long duration especially in patients with persisted malnutrition**.**

The limitation of this study is that it was conducted in a single center. The data of PD prescription, dialysis adequacy, residual renal function, and the use of diuretics, angiotensin-converting enzyme inhibitor, and angiotensin II receptor blockers were not included in our analysis. We suggest that potassium levels should be closely monitored closely among patients with malnutrition. The causes of malnutrition in each patient should be addressed and corrected to reduce the incidence of hypokalemia.

Conclusion

Hypokalemia is associated with poor nutritional status. Patients aged older than 60 years at the start PD, female gender, BW less than 45 kg, had preexisting diabetes, preexisting poor nutritional statushave high risks of developing hypokalemia.

Ethical Clearance: Institutional Ethical Review Committee for Research in Human Subjects of Khon Kaen University for obtaining approval of Chaiyaphum Hospital

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Conflict of Interest: None

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